

[ CASE REPORT ]

## Immunoglobulin G4-related Liver Disease Overlapping with Non-alcoholic Steatohepatitis That Was Diagnosed Simultaneously with Autoimmune Pancreatitis: A Case Report and Review of the Literature

Kotaro Matsumoto<sup>1</sup>, Kentaro Kikuchi<sup>2</sup>, Noriyuki Kuniyoshi<sup>1</sup>, Hiromichi Tsunashima<sup>1</sup>, Katsunori Sekine<sup>1</sup>, Masatoshi Mabuchi<sup>1</sup>, Shinpei Doi<sup>1</sup>, Yoh Zen<sup>3</sup> and Hiroshi Miyakawa<sup>2</sup>

### Abstract:

A 70-year-old woman was referred to our hospital due to symptoms of dry eyes, dry mouth, and epigastric pain. Computed tomography showed distal pancreatic swelling, liver edge dullness and surface irregularities. Serum anti-nuclear antibody titers, immunoglobulin G and IgG4 levels were elevated. Autoimmune pancreatitis (AIP) was diagnosed based on endoscopic findings and a histopathological examination. Her AIP improved after starting prednisolone treatment. A liver biopsy revealed interface hepatitis with lymphoplasmacyte and IgG4-positive plasma cell infiltration. In addition, non-alcoholic steatohepatitis (NASH) was diagnosed based on the presence of parenchymal steatosis, ballooning hepatocytes, and pericellular fibrosis. We experienced a unique liver disease case showing IgG4-related liver disease overlapping with NASH.

**Key words:** autoimmune hepatitis, autoimmune pancreatitis, IgG4-related disease, non-alcoholic steatohepatitis, overlap

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### Introduction

Autoimmune pancreatitis (AIP) is a systemic inflammatory disease characterized by the infiltration of immunoglobulin (Ig)G4-positive plasma cells (1, 2), and it can be complicated by other synchronous or metachronous forms of IgG4-related disease (IgG4-RD) in the hepatobiliary region (3-5). Recently, cases of IgG4-RD involving inflammation, mainly in the liver parenchyma and portal region, as well as IgG4-positive plasma cell infiltration have been reported, and IgG4-related autoimmune hepatitis (IgG4-AIH) is representative of these conditions. However, the number of reported cases of IgG4-AIH is small, so this entity is still being investigated.

In the present case, IgG4-AIH was suspected because the patient had a revised International Autoimmune Hepatitis Group score of 16 points and high serum IgG4 levels, and

IgG4-positive plasma cell infiltration was detected in the portal region. Furthermore, based on the patient's histological findings, it was considered that non-alcoholic steatohepatitis (NASH) had caused liver cirrhosis.

No cases in which IgG4-RD overlapped with NASH-related liver cirrhosis have been reported. We herein report an interesting case and include a consideration of the literature.

### Case Report

In February 2016, a 70-year-old woman became aware that she had dry eyes and a dry mouth. In addition, she had been suffering from epigastric pain since May 2015. She visited a nearby clinic and underwent an examination to investigate the cause of her abdominal symptoms. Gastrointestinal endoscopy showed esophageal varices (Li, F1, Cb, RC-) but no abnormal findings in the gastroduodenal mu-

<sup>1</sup>Department of Gastroenterology, Teikyo University Mizonokuchi Hospital, Japan, <sup>2</sup>Fourth Department of Internal Medicine, Teikyo University Mizonokuchi Hospital, Japan and <sup>3</sup>Department of Diagnostic Pathology, Kobe University Graduate School of Medicine, Japan

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Correspondence to Dr. Kentaro Kikuchi, kentaro@med.teikyo-u.ac.jp

**Table 1. Laboratory Data on Admission.**

Peripheral blood		Blood chemistry		Blood coagulation factors	
WBC	6,010 / $\mu$ L	TP	6.8 g/dL	PT	90.0 %
Neutro	49.8 %	Alb	3.6 g/dL	APTT	35.5 sec
Eos	17.3 %	T-Bil	1.0 mg/dL	Fib	266 mg/dL
Baso	0.8 %	AST	29 U/L	FDP	1.8 $\mu$ g/mL
Mono	5.5 %	ALT	27 U/L		
Lymph	26.6 %	LDH	169 U/L	Serological tests	
RBC	410 $\times$ 10 <sup>4</sup> / $\mu$ L	ALP	284 U/L	IgA	331 mg/dL
Hb	12.1 g/dL	$\gamma$ -GTP	43 U/L	IgM	104 mg/dL
Plt	12.1 $\times$ 10 <sup>4</sup> / $\mu$ L	Amyl	75 U/L	IgG	1,837 mg/dL
		P-Amyl	29 U/L	IgG4	558 mg/dL
Virus markers		T-Chol	152 mg/dL	RF	39 U/mL
HBs-Ag	(-)	TG	81 mg/dL	ANA	$\times$ 80 (homo, speckled)
HBs-Ab	(-)	UN	9.6 mg/dL	Anti-SSA antibody	(-)
HBe-Ag	(-)	Cr	0.60 mg/dL	Anti-SSB antibody	(-)
HBe-Ab	(-)	Na	141 mEq/L	AMA-M2	(-)
HBe-Ab	(-)	K	4.2 mEq/L	Anti-LKM1 antibody	(-)
HBe-Ab	(+)	Glu	95 mg/dL	Hyaluronic acid	69.2 ng/mL
HBV-DNA	(-)	HbA1c (N)	6.4 %	Type IV collagen-7S	6.2 ng/mL
HBcrAg	$\leq$ 2.9	CRP	0.04 mg/dL	HLA	DR8, DR15
HCV-RNA	(-)				

$\gamma$ -GTP:  $\gamma$ -glutamyltransferase, Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AMA-M2: anti-mitochondrial M2 antibody, Amyl: amylase, ANA: antinuclear antibody, Anti-LKM1: anti-liver kidney microsome 1 antibody, Anti-SSA: anti-Sjögren's syndrome-related antigen A, Anti-SSB: anti-Sjögren's syndrome-related antigen B, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, Baso: basophils, Cr: creatinine, CRP: C-reactive protein, Eos: eosinophils, FDP: fibrin/fibrinogen degradation products, Fib: fibrinogen, Glu: glucose, Hb: hemoglobin, HbA1c (N): glycated hemoglobin, HBe-Ab: hepatitis B core antibody, HBcrAg: hepatitis B virus core-related antigen, HBe-Ab: hepatitis B envelope antibody, HBe-Ag: hepatitis B envelope antigen, HBs-Ab: hepatitis B surface antibody, HBs-Ag: hepatitis B surface antigen, HBV-DNA: hepatitis B virus DNA, HCV-RNA: hepatitis C virus RNA, HLA: human leukocyte antigen, IgA: immunoglobulin A, IgG: immunoglobulin G, IgG4: immunoglobulin G4, IgM: immunoglobulin M, K: potassium, Lymph: lymphocytes, LDH: lactate dehydrogenase, Mono: monocytes, Na: sodium, Neutro: neutrophils, P-Amyl: pancreatic amylase, Plt: platelet count, PT: prothrombin time, RBC: red blood cell count, RF: rheumatoid factor, T-Bil: total bilirubin, T-Chol: total cholesterol, TG: triglycerides, TP: total protein, UN: urea nitrogen, WBC: white blood cell count

cosa. Abdominal computed tomography (CT) revealed swelling of the distal pancreas, liver edge dullness, and liver surface irregularities. Therefore, the patient was referred to our gastrointestinal medicine outpatient facility for a further examination and treatment.

She had a history of hypertension, arrhythmia, and spinal canal stenosis, which had been treated with telmisartan, nifedipine CR, verapamil, and pregabalin. She was not consuming any dietary supplements. She had no history of blood transfusions, no remarkable family history, and no history of autoimmune disease and did not consume significant amounts of alcohol or smoke.

Upon admission, a physical examination showed spontaneous epigastric pain and obesity (body mass index: 31.2). Swelling of the salivary and lacrimal glands was not seen. Regarding ophthalmology, corneal disorders were not seen, but the Schirmer test demonstrated that the patient's tear volume was reduced [3 mm (severe dry eye:  $<$ 5 mm) wetting of the paper after 5 minutes]. The results of her laboratory tests are shown in Table 1. Her total white blood cell count was within the normal limits, although eosinophilia was detected. Her platelet count was 12.1 $\times$ 10<sup>4</sup>/ $\mu$ L (reference range: 13-36 $\times$ 10<sup>4</sup>), and her glycated hemoglobin (HbA1c) level was 6.4% (reference range: 4.6-6.2%). Her prothrom-

bin time and aspartate aminotransferase, alanine aminotransferase, total bilirubin, and pancreatic amylase levels were within the normal limits. A test for the hepatitis B virus core antibody produced a positive result; however, tests for hepatitis B virus DNA and hepatitis B virus core-related antigen both produced negative results. No hepatitis C virus RNA was detected in the patient's serum by polymerase chain reaction. The patient's anti-nuclear antibody (ANA) titer was 1:80, and the homogeneous and speckled ANA patterns were seen. The patient's rheumatoid factor level was elevated to 39 U/mL (reference range:  $\leq$ 15). Tests for the anti-liver/kidney microsome type 1 antibody and anti-mitochondrial M2 antibody produced negative results. The patient's serum IgG level was elevated to 1,837 mg/dL (reference range: 870-1,700 mg/dL), and her serum IgG4 level was 558 mg/dL (reference range: 4.5-117 mg/dL). The patient's type IV collagen-7s domain level was mildly elevated to 6.2 ng/mL (reference range:  $\leq$ 6 ng/mL), and her hyaluronic acid level was 69.2 ng/mL (reference range:  $\leq$ 50 ng/mL). The human leukocyte antigen (HLA) test detected DR8 and DR15. Contrast-enhanced CT (Fig. 1a) showed findings that were indicative of liver cirrhosis; i.e. the margins of the liver were blunted, the liver surface was irregular, and diffuse distal pancreatic swelling and a capsule-like



**Figure 1.** Imaging findings obtained using contrast-enhanced computed tomography (CECT), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS). (a) CECT showed findings that were indicative of liver cirrhosis, e.g. the margins of the liver were blunted, the liver surface was irregular, and diffuse distal pancreatic swelling and a capsule-like rim were seen. (b) ERCP showed diffuse irregular narrowing of the distal main pancreatic duct and no abnormalities in the extrahepatic bile ducts. (c) EUS showed that some parts of the parenchyma of the distal pancreas were hypoechoic and lobulated, whereas other parts were swollen and exhibited a hyperechoic patchy/mesh-like appearance.

hepatic rim were seen. Endoscopic retrograde cholangiopancreatography (Fig. 1b) showed diffuse irregular narrowing of the distal main pancreatic duct. Endoscopic ultrasound (EUS) (Fig. 1c) showed that parts of the parenchyma of the distal pancreas were hypoechoic and lobulated, whereas other parts were swollen and exhibited a hyperechoic patchy/mesh-like appearance. An EUS-fine-needle aspiration biopsy specimen showed marked lymphoplasmacytic cell and IgG4-positive plasma cell infiltration [ $\geq 10$  cells per high-power field (HPF)] in the pancreas (Fig. 2a, b). No marked storiform fibrosis or obliterative phlebitis was observed.

A liver biopsy revealed severe interface hepatitis together with lymphoplasmacytic cell infiltration (Fig. 2c, d), 40 IgG4-positive plasma cells/HPF in the portal region (Fig. 2e). Furthermore, mild liver parenchymal inflammation and steatosis (covering about 10% of the liver) (Fig. 2f), ballooning hepatocytes (Fig. 2g), pericellular fibrosis, and bridging fibrosis (Fig. 2h) were seen, whereas no intrahepatic destruction; concentric periductal fibrosis (“onion skin”), which is suggestive of primary sclerosing cholangitis (PSC); or storiform fibrosis or obliterative phlebitis, which are characteristics of IgG4-RD, was noted. No multinucleated giant cells were observed.

A lip biopsy revealed slight fibrosis and lymphocytic infiltration (containing approximately 50 lymphocytes per 4 mm<sup>2</sup>) focally around the small salivary gland. It was suspected that the patient might have been complicated with Sjögren’s syndrome.

The patient’s clinical and pancreatic histological findings met the 2011 clinical diagnostic criteria for AIP (segmental AIP). AIH was considered pathologically based on the existence of interface hepatitis combined with lymphoplasmacytic cell infiltration, and the patient’s revised International Autoimmune Hepatitis Group score was 16 points (AIH, definite). IgG4 immunohistochemical staining revealed 40 IgG4-positive plasma cells/HPF in the portal region. In addition, NASH was diagnosed based on the detection of paren-

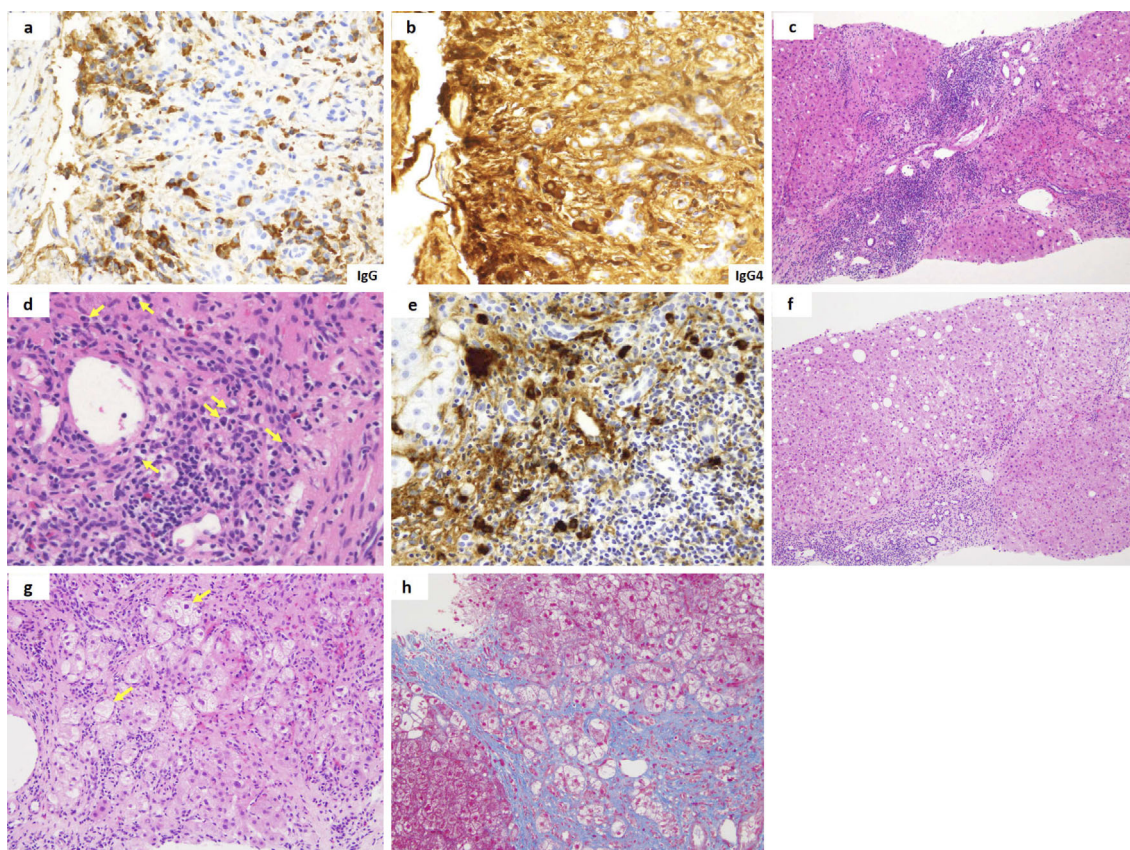
chymal steatosis, ballooning hepatocytes, and pericellular fibrosis. Therefore, we considered that the patient was suffering from AIP combined with IgG4-RD overlapping NASH.

Steroid therapy involving a daily dose of 40 mg of prednisolone for AIP was started. The patient’s serum levels of IgG and IgG4 immediately decreased and soon approached the normal limits. In addition, an imaging study indicated that the distal pancreatic swelling had improved. The prednisolone treatment was eventually discontinued after being tapered, and the patient’s condition has not recurred.

## Discussion

IgG4-RD is a systemic disease, while AIP is the most common of its organ-specific manifestations (pancreatic disease is seen in 60% of patients with IgG4-RD) (2). Furthermore, AIP is often complicated with hepatobiliary conditions, including PSC, inflammatory pseudotumors, and chronic active hepatitis (3-5). IgG4-related sclerosing cholangitis (IgG4-SC) is a representative IgG4-RD and most frequently occurs in combination with AIP. In the current case, no marked liver dysfunction was seen in blood tests. However, a histological examination of a liver biopsy sample was carried out, due to the possibility of AIH (i.e., the patient was ANA-positive and exhibited elevated serum IgG levels). The liver biopsy specimen showed interface hepatitis combined with lymphoplasmacytic cell infiltration, and the patient was confirmed to have AIH based on her revised International Autoimmune Hepatitis Group score (16 points; a score of  $\geq 16$  points indicates AIH, definite). Although the marked inflammatory cell infiltration and hepatocyte collapse seen in the portal region and liver parenchyma were suggestive of AIH, AIP often exhibits a portal inflammation pattern or lobular hepatitis characterized by parenchymal inflammation and focal necrosis (6).

Recently, cases of IgG4-RD without storiform fibrosis and obliterative phlebitis, which are characteristics of IgG4-RD, have been reported, and IgG4-AIH and IgG4 hepatopathy



**Figure 2.** Histopathological findings of the pancreas (a, b) and liver biopsies (c-h). (a, b) Marked lymphoplasmacytic cell infiltration and marked immunoglobulin G4 (IgG4) -positive plasma cell infiltration was seen in the pancreatic parenchyma. (a) (IgG staining, magnification:  $\times 400$ ), (b) (IgG4 staining, magnification:  $\times 400$ ). (c, d) Severe interface hepatitis combined with lymphoplasmacytic cell infiltration. (c) [Hematoxylin and Eosin (H&E) staining, magnification:  $\times 100$ ], (d) Lymphoplasmacytic cell (arrows) (H&E staining, magnification:  $\times 400$ ). (e) Detection of IgG4-positive plasma cells. Forty IgG4-positive plasma cells/high-power field were detected in the portal region (IgG4 staining, magnification:  $\times 400$ ). (f) Mild liver parenchymal inflammation and steatosis (H&E staining, magnification:  $\times 100$ ). (g) Ballooning hepatocytes (arrows) (H&E staining, magnification:  $\times 400$ ). (h) Pericellular fibrosis and bridging fibrosis (Masson's trichrome staining, magnification:  $\times 200$ )

have been suggested to be representative of these conditions (4-12). Umemura et al. (5) were the first to propose the existence of IgG4-AIH, and they subsequently reported two further cases of the condition (5, 7, 8). Ishizu et al. (9) reported a case of IgG4-AIH involving metachronous type 1 AIP, and Suto et al. (11) and Araki et al. (12) each reported one case of IgG4-AIH without other synchronous or metachronous forms of IgG4-RD. Therefore, to our knowledge, six cases of IgG4-AIH, including our own, have been reported in Japan.

Among these cases, the male-to-female ratio was 2:4, and the patients' median age was 59.5 years old (range: 42-73 years old). HLA-DR4, which exhibits a strong correlation with AIH, was found in one case. Synchronous or metachronous IgG4-RD complications were encountered in three cases (two cases involved type 1 AIP, and one case involved IgG4-SC). Prednisolone was administered as a treatment in all of these cases (Table 2).

Umemura et al. (8) proposed the diagnostic criteria for

IgG4-related AIH as follows: 1) having definite AIH according to the International Autoimmune Hepatitis Group (IAIHG) scoring system, 2) serum IgG4 concentration  $\geq 135$  mg/dL, and 3) immunostaining of IgG4 showing  $\geq 10$  IgG4-positive plasma cells/HPF in the portal tract. Nakanuma et al. (10) recommended the following criteria: 1) serum IgG4 concentration  $\geq 135$  mg/dL, 2) immunostaining of IgG4 showing  $\geq 10$  IgG4-positive plasma cells/HPF in liver tissue, 3) chronic hepatitis with zonal and bridging necrosis or broad collapse, and 4) other metachronous or synchronous IgG4-related disease(s). Although Chung et al. (13) and Aydemir et al. (14) also reported cases of IgG4-AIH, they did not use a high serum IgG4 concentration, one of the major diagnostic items for IgG4-RD, as a diagnostic criterion; therefore, the conditions they reported might have been different from the IgG4-AIH described by Umemura et al. and Nakanuma et al. The current case met the diagnostic criteria of Umemura et al. and would have been classified as possible IgG4-associated AIH according to the diagnostic criteria

**Table 2. List and Clinical Features of Reported IgG4-AIH Cases.**

No.	References	Age	Sex	ANA	Serum IgG	Serum IgG4	IgG4 plasma cells/HPF or IgG4/IgG cell ratio	Revised International Autoimmune Hepatitis Group score	HLA-DR	Synchronous or metachronous IgG4-RD	Treatment
1	(5)	54	F	×80	2,403	557	≥30 IgG4+ plasma cells/HPF	18 (definite)	DRB1(*1302 and *1501)	IgG4-SC	40 mg PSL/day
2	(7)	42	M	×20,480	5,622	642	≥30 IgG4+ plasma cells/HPF	definite	DRB1(*0405)	(no disease)	60 mg PSL/day
3	(9)	73	M	×2,560	2,850	284	30-40 IgG4+ plasma cells/HPF	18 (definite)	DRB1(*1302 and *1502)	type 1 AIP	40 mg PSL/day
4	(11)	48	F	×40	1,538	669	25.8 IgG4+ plasma cells/HPF	21 (definite)	DR1, DR15	(no disease)	30 mg PSL/day + 600 mg UDCA
5	(12)	65	F	×10,240	3,262	535	IgG4/IgG cell ratio: 85%	20 (definite)	DR8, DR15	(no disease)	50 mg PSL/day
6	This case	70	F	×80	1,837	558	40 IgG4+ plasma cells/HPF	16 (definite)	DR8, DR15	type 1 AIP	40 mg PSL/day

AIH: autoimmune hepatitis, AIP: autoimmune pancreatitis, ANA: anti-nuclear antibody, F: female, HLA: human leukocyte antigen, HPF: high-power field, IgG: immunoglobulin G, IgG4: immunoglobulin G4, IgG4-RD: immunoglobulin G4-related disease, M: male, PSL: prednisolone, SC: sclerosing cholangitis, UDCA: ursodeoxycholic acid

of Nakanuma et al.

Umamura et al. also reported that IgG4 hepatopathy causes liver damage in 60-70% of AIP cases (6). In the present case, a hepatopathological examination showed as many as 40 IgG4-positive plasma cells/HPF in the portal region and an IgG4/IgG-positive cell ratio of >40%; however, the possibility of IgG4 hepatopathy should be considered because zonal and bridging necrosis, which are characteristic findings of the IgG4-AIH proposed by Nakanuma et al., were not seen. Furthermore, liver cirrhosis due to NASH [grade 1, stage 4 according to the classification of Brunt et al. (15)] was suspected because mild liver parenchymal inflammation, steatosis, ballooning hepatocytes, Mallory bodies, pericellular fibrosis, and advanced fibrosis (pseudolobule formation and bridging fibrosis) were noted. It was reported that about half of NASH patients are ANA-positive (16, 17), and Yatsuji et al. (18) reported that 97% of Japanese female non-alcoholic fatty liver disease (NAFLD) patients exhibited revised International Autoimmune Hepatitis Group scores of ≥10 points (indicating AIH, probable or definite). It is difficult to distinguish NASH from AIH, as the revised International Autoimmune Hepatitis Group scoring system does not include criteria for excluding NASH. Furthermore, a few cases of NAFLD that overlapped with AIH have been reported (19-22). Clinicians should keep overlapping NASH and AIH in mind in cases involving ANA positivity, an AIH score of ≥10 points, and/or difficulty in pathological differentiation. In cases in which active hepatitis is caused by NASH, the administration of prednisolone might exacerbate the liver damage; therefore, histopathological examinations of liver biopsy samples are important for determining the optimal treatment strategy.

The current case involved an obese patient, and liver cirrhosis due to NASH was suspected because of pericellular fibrosis, disseminated ballooning hepatocytes, and the pres-

ence of very few central veins, which suggest previous lobule-centered inflammation. However, the degree of liver inflammation was severe based on the presence of IgG4-positive plasma cell infiltration. Therefore, we considered that the observed inflammation was due to IgG4 hepatopathy or IgG4-AIH overlapping with AIP, on a background of NASH cirrhosis. We continued to treat the patient with prednisolone for her AIP. Long-term and high-dose glucocorticoid therapy carry a risk of exacerbating NASH; however, no liver damage suggesting the exacerbation of NASH occurred during the prednisolone treatment.

Although there have been several reports of NASH complicated by autoimmune diseases (23-25), there have not been any reported cases of NASH complicated by IgG4-related disease, autoimmune pancreatitis, or IgG4-related liver disease. The pathogenesis of NASH-induced autoimmune diseases has not been elucidated in detail and will be the topic of future discussion. However, the involvement of IL-17 is assumed as an element common to both NASH and autoimmune diseases. In recent years, it has become known that IL-17 produced by Th17 cells, a kind of Th cell, induces autoimmune diseases such as psoriasis, rheumatoid arthritis, Crohn's disease, and many others (26). In particular, Th17 cells are frequently found in the intestinal lamina propria, and it has recently been clarified that the induction of Th17 cells involves the presence of enterobacteria, such as segment bacteria. Primarily, Th17 cells enhance the gastrointestinal mucosal barrier function by producing IL-22, which is an antimicrobial peptide inducer, in addition to IL-17, which promotes the migration of leukocytes. However, it has been reported that the overactivation of Th17 cells is closely related to the pathogenesis of autoimmune diseases. In addition, the involvement of Th17 cells and IL-17 has been reported in several animal models of NAFLD progressing to NASH (27-31). Tedesco et al. (32) reported the devel-

opment of liver fibrosis and inflammation requires hepatic activation of  $\gamma\delta$  TCR<sup>+</sup> cells and production of IL-17 mediated by exposure to *Lactobacillus gasseri* that is translocated to the liver due to increased intestinal permeability in *Mdr2*<sup>-/-</sup> mice. It is thought that dysbiosis, which is one of the pathogenesises of NASH, causes the proliferation and activation of Th17 cells and induces the overproduction of IL-17, thereby leading to autoimmune diseases.

This case was difficult to distinguish from AIH because of the existence of NASH in the background. This is the first reported case of NASH overlapping with IgG4-RD, and it will be necessary to accumulate and consider further cases in the future.

**The authors state that they have no Conflict of Interest (COI).**

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